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ERRATUM

Vol. 9, No. 7, page 201, column 1, 2nd paragraph, line 23:
24 *should read* **54**

NUTRITION REVIEWS

VOL. 9 SEPTEMBER, 1951 No. 9

NUTRITIONAL PROBLEMS OF PATIENTS WITH BURNS

During World War II it was evident that malnutrition developed rapidly in previously well-nourished wounded soldiers, and that under this circumstance morbidity was prolonged and mortality increased. Patients with severe thermal burns presented some of the most difficult nutritional problems.

Burns were responsible for more than half of the fatal casualties and probably at least three-quarters of all the casualties at Hiroshima and Nagasaki. Thermal burns, then, will be one of the most important types of injury in any future war. However, it should be stressed that in the event of atomic bomb explosions, combined radiation and thermal injuries will be frequent.

Not all patients with burns present significant nutritional disturbances. In general, the abnormalities depend on the severity of the injury and the status (age, sex, nutrition, etc.) of the individual at the time of injury. Minor nutritional problems are encountered in patients, previously in good health, with superficial second degree burns, despite large areas of skin injured.

Deep burns (particularly of the "wet" necrosis variety) may lead to marked nutritional disturbances. Healing of deep burns is different from healing of superficial burns. Sloughing (or excision) of the dead skin, followed by granulation of the uninjured deeper tissue must occur. If the granulation area is of any significant size, skin coverage cannot take place spontaneously. Skin grafting must be carried out. If the patient is maintained in good nutritional state, granulation tissue appears firm, red, and healthy, skin grafts take well, and donor sites heal uneventfully. Even if the area burned is very extensive, healing can take place if the patient is maintained in good nutrition and if infection is controlled.

If the patient with deep burns becomes malnourished (and malnutrition may develop very rapidly), serious complications ensue. Wound healing is delayed, infection is more serious, morbidity is prolonged, and mortality is increased. Granulation tissue in such patients is markedly different from that seen in well-nourished patients—granulations may be absent, or when present, are soggy, gray, and extremely friable. Skin grafts do not take over such areas nor do donor sites heal.

Regarding the pathogenesis of the nutritional depletion often seen following severe burns, inadequate intake is, in general, one of the most important and frequent factors. The seriously injured patient often has a poor appetite, engendered, in part, by apprehension, pain, and oversedation. Further, alterations in gastrointestinal function may be seen early following severe burns, particularly if shock is present, and this further complicates maintenance of good nutrition.

Disturbances in the metabolism of all nutrients so far studied are seen in the seriously burned patient. Many of the changes are similar to those following other types of injury, for example, femoral fractures. Although fair amounts of descriptive data on plasma concentrations and urinary excretions of various metabolites have been accumulated, there are significant gaps in the available data and many fundamental questions remain unanswered.

Little data are available as to total oxygen consumption by the burned patient. Superficial and scanty observations suggest that the metabolic rate is increased, but quantitative information as to the extent, duration, etc. of the elevation is not at hand. No data are available on the metabolic rate of specific tissues in burned patients.

Most of the studies on metabolic changes following thermal burns have dealt with the

problem of protein metabolism. It is well established that significant protein depletion occurs in patients with severe burns. There is a variable loss of nitrogenous compounds from the burned area depending upon: (a) depth of burn; (b) extent of burn; (c) infection.

In addition to the loss of nitrogenous products from the burned surface, there is an increased urinary excretion of nonprotein nitrogen beginning three or four days after burns, reaching a peak during the first or second week and persisting for three or four weeks. By and large, the intensity of the reaction parallels the severity of the injury, and is shown most markedly by previously well-nourished young adult males. It is less in females and children and very little in individuals who were previously poorly nourished.

Disturbances in water and electrolyte metabolism are marked following thermal injury. The changes in water distribution, for example, the early "loss" of fluid into, adjacent to, and from the burned area, and the consequent reduction in the circulating blood volume, have long been recognized. There is a decrease in serum sodium and chloride in the early post-burn period and a shift of some sodium into injured cells with a concomitant shift out of an equivalent amount of potassium. Sodium and chloride balances are initially positive, but later during the period of resorption of wound edema and diuresis these balances become negative. Sodium lost from the surface may comprise most of the sodium losses. The urinary loss of chloride may be higher and the exudate loss lower.

In human beings a negative potassium balance of 2 to 5 g. daily for the initial two to three days has been described. A positive balance is promptly obtained as oral potassium intake is recommenced. There is little correlation between nitrogen and potassium balance, since positive potassium balance is regained several days to weeks prior to positive nitrogen balance. Exudate potassium comprises at a maximum but 20 per cent of the total potassium loss.

Data in regard to minerals other than sodium, potassium, and chloride are almost completely lacking.

Derangement in carbohydrate metabolism is frequently seen following burns. Increased blood sugar and lactic acid and lowered carbon dioxide-combining power usually appear soon after injury and persist over a period of days. It would appear that there is a marked increase in gluconeogenesis and in peripheral carbohydrate breakdown. Inadequate data are available regarding glucose and insulin tolerances of burned patients.

There are insufficient data available as to vitamin metabolism and requirements in patients with burns. In fact, no data are available regarding fat-soluble vitamins, and only meager information is available regarding certain of the water-soluble vitamins. There are more reports of ascorbic acid metabolism than of any of the other vitamins. Decrease in plasma ascorbic acid concentration, urinary excretion, and in "saturation" as measured by intravenous "load test" have been described. Similar changes in urinary excretion and "saturation" have been reported in regard to riboflavin, thiamine, and nicotinamide.

Some disturbance of liver function is not uncommon in extensively burned patients, particularly if shock has been severe. Increased bromsulfalein retention, increased urine urobilinogen excretion, increased serum bilirubin concentration, abnormal cephalin flocculation, and increased prothrombin time have been described. These changes are most marked in the early period following burns, and are related to the severity of the burn.

There is considerable evidence indicating changes in adrenal activity following burns and many of the metabolic changes are thought to be due, in part, to varying adrenal activity. An early increased secretion of epinephrine is likely. Depletion of cortical lipoid, particularly cholesterol, following burns has been described together with a con-

comitant fall in adrenal ascorbic acid concentration. There is an early increase in 17-ketosteroid excretion followed by a lowered excretion until convalescence is essentially complete. A high 11-oxysteroid excretion has been observed continuously following injury.

An imbalance of adrenal hormonal activity has been postulated, such that there is a brief period of increased nitrogen and sugar hormonal activity, followed quickly by an increase in the sugar hormonal function and a concomitant decrease of the nitrogen hormonal effect. This would result in increased gluconeogenesis from nitrogenous compounds with a consequent increase in urinary nitrogen excretion. In keeping with this theory is the high blood sugar concentration found during this period. Activation of the sympathetic nervous system and the pituitary is thought to occur following burns. The changes in adrenal activity are probably mediated in part through changes in pituitary action. The pituitary gland itself has not been adequately studied.

No specific lesions have been reported as occurring in the pancreas, thyroid, or other glands of internal secretion. However, special histologic technics have not been utilized.

It is apparent that widespread metabolic changes with consequent disturbances in nutrition follow thermal burns. Despite numerous investigations, however, much is yet to be learned. Most of the data available are of a descriptive nature, and many fundamental questions remain unanswered. In particular, knowledge about specific tissue metabolism is needed, together with more detailed studies of intermediary metabolism. More information is needed regarding the physiologic and clinical sequelae of the "reaction to injury."

Regarding the practical nutritional care of patients with severe thermal injuries, we know, in a general way, that the requirements of such patients are higher than those of normal individuals—and that fairly high dietary intakes should be begun early. But we do not know how much higher, and specifically, what the quantitative relationships of the various metabolites should be. Nor do we know the optimal timing for the feeding regimens except that, as a generality, prophylaxis is preferable to (and easier than) therapy. The nutritional requirements must be anticipated and met before severe malnutrition occurs.

The therapy of burn shock will not be detailed, although it, of course, is important in the nutrition of the burned patient. Administration of blood, plasma, albumin, electrolytes, water, carbohydrate, vitamins, etc. is important. Attention should, however, be called to the almost complete lack of information available regarding the metabolism of some of the colloids suggested for the treatment of shock.

It is obvious that the food provided must be a complete metabolic mixture, containing adequate amounts of protein, carbohydrate, fat, minerals, water, and accessory food substances. If possible the nutritional demands should be met by oral feeding. If this is not possible, gastric, jejunal, and parenteral feedings, singly and in combination, must be carried out. It should be stressed again that the optimum quantities and proportions of the various foodstuffs have not yet been established.

Some investigators believe that high intakes should not be started early after injury. However, we believe that if the malnutrition can be averted in part by early high food intakes, it seems logical to do so. Children receiving from the start an intake one and a half times that recommended by the National Research Council as optimal for normal children remain in excellent nutritional status following severe burns. Male adults (previously well) receiving an intake of 1.5 g. of protein and 45 calories per kilogram of body weight from the start show nutritional depletion if the burns are severe—but less than if this intake is not begun very early.

Oral intakes begun at these levels on the first or second day of injury are well toler-

ated. If there is a delay of a few days, then gastrointestinal upsets are much more common. Continuous gastric drip feedings may be better tolerated early than the usual oral feedings. Early intakes at a level of 70 calories and 2 g. of protein per kilogram of body weight have not been tolerated by some adult patients.

It has been found useful to place the major emphasis on high protein, high caloric, high vitamin, liquid diets. This is apt to prove the most practical and useful method of feeding mass casualties. A reasonably palatable mixture that contains all the food elements needed over long periods of time is necessary. In both the oral and tube feedings which we use, 20 to 45 per cent of the calories are supplied by fat, often by an emulsified preparation. This is considerably higher than most investigators have recommended for seriously burned patients. The effect of this diet is under investigation.

Forcing the diet orally or by tube may not always be beneficial. Nausea, vomiting, distention, and diarrhea are limiting factors. Under these conditions supplementation by the intravenous route is indicated.

The effects of various hormones, for example, testosterone, adrenocorticotropic (ACTH), cortisone, and thyroxine, are under intensive investigation.

At the present time it is not possible to outline with certainty the nutritional care of patients with radiation injury; there simply is not enough information at hand. The data available suggest, in general terms, that individuals in good nutritional status at the time of injury resist radiation injury better than those in poor nutritional states; that morbidity and mortality are less in individuals whose nutritional states are maintained at high levels after injury.

However, the optimum quantities and proportions of the various foodstuffs needed have not yet been established. In patients with combined thermal and radiation injury, it probably will not be possible to feed the patient orally to the same extent as patients with only burns, in view of the marked gastrointestinal upsets following radiation injury. Antibiotics are definitely therapeutically useful. Their effects on nutrition have yet to be determined.

In conclusion, present knowledge of the specific nutritional requirements of patients with thermal and/or radiation injury is incomplete in many essentials. It is hoped that significant advances will be made in the next few years.

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EFFECT OF COMPOUND F IN MAN

Certain fairly constant metabolic changes are noted following administration of adrenocorticotropic hormone (ACTH). Among these are leukopenia and eosinopenia (decrease in white blood cells and red blood cells), glycosuria, increased urinary total nitrogen, creatinine and amino acid excretion, increased potassium excretion, and a variable sodium retention. More prolonged administration often leads to hypertension, insulin-resistant diabetes and a change in facial expression suggesting Cushing's syndrome (*Nutrition Reviews* **7**, *290* (*1949*); **8**, *173* (*1950*)).

The metabolic effect of ACTH has not been duplicated entirely by any one of the three adrenocortical hormones so far studied: compound E, or cortisone (17-hydroxy-11-

dehydrocorticosterone), injections of which lead to gluconeogenesis from protein catabolism with minimal sodium-retaining properties; desoxycorticosterone, which has no carbohydrate or protein effect but is potent in producing retention of sodium; and the postulated "N" hormone, which accounts for the opposite effect of cortisone, *i.e.*, it stimulates protein anabolism and presumably has an androgenic effect as well, and thus resembles testosterone.

Some doubt has been raised that any one of these hormones is secreted by the adrenal cortex under pituitary stimulus. In fact, it has been suggested that another hormone with effects combining those of cortisone and desoxycorticosterone is secreted and accounts for the activities of the two distinct compounds. Investigation of Kendall's compound F (17-hydroxy-corticosterone) suggests that it may combine these two effects.

P. H. Forsham, G. W. Thorn, F. T. G. Prunty, and A. G. Hills (*J. Clin. Endocrinol.* **8,** *15 (1948)*) found that 20 mg. of compound F produced the same eosinopenic effect and increase in uric acid excretion observed following administration of ACTH. Because the compound is not readily available, further studies have been few. P. Fourman *et al.* (*J. Clin. Invest.* **29,** *1462 (1950)*) studied the effect of 50 mg. of compound F administered twice, *i.e.*, on days three and six of a twelve-day experiment, to a normal individual on a constant diet under controlled conditions. The diet was said to furnish 2910 calories composed of 300 g. of carbohydrate, 125 g. of fat, 123 g. of protein, and 13 g. of alcohol. Urine collections and determinations were made every two hours on days three and six and every four hours on other days except at night, when eight-hour collections were made.

The subject showed a slight decrease in urine volume and gain in weight immediately following each injection, both of which reverted to the control level two days after the injection. There was no significant change in blood pressure during the experimental period. Glycosuria appeared following each injection of compound F and persisted for two weeks after the second injection. The glycosuria was not associated with hyperglycemia nor with an abnormal glucose tolerance (this test was done a week after the last injection). The authors therefore suggest that it is related to a lowered renal threshold for glucose rather than evidence of gluconeogenesis. As in the studies of Forsham *et al.* (*loc. cit.*) eosinopenia followed each of the two injections of compound F; lymphopenia likewise occurred.

A slight increase in urinary excretion of nitrogen followed injection of compound F on both occasions compared with the preinjection control period for the first injection and a postinjection period following the second injection. Retention of nitrogen did not appear again until the third day after the injection. A marked increase in potassium excretion followed both injections of compound F. The increase lasted about one day and was followed by a day in which the potassium excretion was about the same as in the control period and then by a day in which potassium retention occurred. The authors point out that increased excretion of potassium was far out of proportion to the breakdown of protoplasm calculated from the increased nitrogen excretion.

The data on sodium and water metabolism were difficult to interpret because of changes during the control period. Nevertheless, it appeared that administration of compound F led to a retention of both sodium and water which were later lost as the effect of the hormone disappeared. These changes in sodium, potassium, and chloride in addition closely resembled those which previously had been found following administration of desoxycorticosterone.

The authors note that these results compare well with those observed following administration of ACTH and suggest that

since compound F reproduces fairly well both the "S" hormone-like action and the desoxycorticosterone-like action of the adrenal cortex, its action may explain with one adrenal cortical hormone, the effect of the administration of ACTH.

IMPROVING ALFALFA FOR MORE HEALTHY LIVESTOCK

For almost a decade considerable interest has been shown in finding a method of preserving more completely, and in an economically and nutritionally practical fashion, the high carotene content of alfalfa in hay and meal products. Although these efforts have not yet been successful, much has been learned of the variation to be found in carotene content of alfalfa. Variety differences have been studied by W. E. Ham and H. M. Tysdal (*J. Am. Soc. Agronomy* **38,** *68 (1946)*). Among 7 lines that were not damaged by leaf hoppers they found a considerable range of carotene content, indicating the possibility of developing strains higher in carotene content. They pointed out that since 77 per cent of carotene is in the leaves, breeding for resistance to leaf hoppers and to all leaf diseases, and for a higher percentage of leaves, would tend to improve the nutrient value of the crop. In many mixed feeds alfalfa meal richer in carotene, and particularly in stable carotene, would be extremely valuable.

C. R. Thompson (*Agronomy J.* **41,** *294 (1949)*) investigated several varieties of alfalfa and the time of sampling (time of day and stage of growth) to determine the optimum starting material for dehydration or field curing operations. Nine varieties were grown in Missouri. Fresh samples were steam blanched, frozen, and later analyzed. These samples were taken at normal time for two cuttings. Carotene ranged from 235 to 309 parts per million (p.p.m.) (dry basis). Ladak was highest and Turkistan lowest. Other varieties were fairly consistent in their order between the extremes. Three varieties were analyzed from the Imperial Valley, California. Varieties India, California Common and Africa, ranging from 330 to 350 p.p.m., were uniformly higher in carotene content than the Missouri samples. Leafier parts of the plant had higher values than the stem portions.

California Common alfalfa was then studied in more detail at Riverside, California. Three types within this variety, separated on the basis of stem color and leaf shape, varied only 12 to 15 per cent from each other in carotene content. At different ages from 10 to 59 days, carotene content decreased with age, due to increasing fiber content. Leaves contained as high as 596 p.p.m. In general, a decrease was found after an early morning sampling. This phase of the subject needs much more work before reliable recommendations can be made relative to cutting time.

C. R. Thompson (*Ind. Eng. Chem.* **42,** *922 (1950)*) has studied the effect of antioxidants on the stability of carotene in alfalfa meal. Meals were sprayed with solutions under test and stored at 65°C. for seven and fourteen days. This is an accelerated storage test to simulate effects that would result under normal storage conditions for much longer periods of time. Fifty-four compounds were tested, including substituted phenylenediamines, amines, phenols, hydroquinones, sulfur compounds, and dihydroquinolines. Several antioxidants gave very favorable results, but metal deactivators failed to produce increased carotene stability. A tertiary alkyl group or the benzyl group in the 2,5 positions on hydroquinone gave increased stability. With p-phenylenediamine either the butyl or phenyl group enhanced the antioxidant activity. Water-soluble compounds were relatively ineffective, indicating the importance of penetration into the site of carotene occurrence.

Problems of toxicity of the antioxidants to the animal consuming the alfalfa meal have not yet been solved, nor has the practicality of such sprays been indicated.

The methione and cystine content of 2 strains of alfalfa were studied in relation to different concentrations of sulfate ion (in sand cultures) by S. L. Tisdale, R. L. Davis, A. F. Kingsley, and E. T. Mertz (*Agronomy J.* **42,** *221* (*1950*)). These amino acids are of particular importance to nonruminant animals. These investigators found that the 2 strains of alfalfa differed in their efficiency of synthesis of the two amino acids, and that these differences tended to be more marked at the lower levels of sulfur nutrition. After studying these 2 clonal lines and their selfed progenies, it was concluded that the contents of these two sulfur-containing amino acids increased with increasing sulfate supply in the nutrient solution, and that a genetic relationship does exist between parent plants and their selfed progeny with respect to content of methionine and cystine. Even at the highest levels of sulfate, the concentrations of these acids were too low to make alfalfa protein a balanced one. Further increases are not to be expected from abnormal sulfur fertilization; they must result from an increased inherent capacity for synthesis brought about by breeding methods.

From these data it would appear that the customary practice of using crude protein as a criterion of forage quality may lead to errors because neither total nitrogen nor total sulfur indicates the fundamental behavior of cystine and methionine. Total nitrogen was highest at low levels of sulfur while contents of methionine and cystine were lowest at these low levels.

Thus fertility studies must consider possible effects of genetic differences, and plant breeding studies must evaluate fertility levels to avoid incorrect conclusions. Alfalfa is such a valuable forage and hay crop and its use so universal that much more effort in the improvement of its product would seem justified.

NIACIN REQUIREMENT AND PROTEIN INTAKE IN INSECTS

When fed in excess of the requirements for protein synthesis, tryptophan can serve as a substitute for niacin in the diet of all higher animals so far investigated (*Nutrition Reviews* **8,** *85*, *211* (*1950*)). For this reason, the effect of increasing the level of protein intake upon the requirement for niacin can scarcely be determined directly, since an increase in any complete dietary protein increases the tryptophan intake to an extent sufficient to decrease the niacin requirement through conversion of the excess tryptophan to niacin. Despite this fact, there are inconclusive indications that the absolute requirement for niacin (*i.e.*, dietary plus synthesized niacin) is increased by an increase in protein intake. Thus, "extra" tryptophan supplied as casein is not utilized for niacin synthesis as efficiently as when the same amount of tryptophan is administered in free form (F. Rosen and W. A. Perlzweig, *J. Biol. Chem.* **177,** *163* (*1949*); O. Olcese, P. B. Pearson, and P. Sparks, *J. Nutrition* **39,** *93* (*1949*)), a possible indication that disposal of the other amino acids fed with the protein-bound tryptophan causes an increased requirement for niacin.

An uncomplicated solution of this problem is provided by investigations of the effect of the protein content of the diet on the niacin requirement of insects (G. Fraenkel and H. R. Stern, *Arch. Biochem.* **30,** *438* (*1951*)). Both *Tenebrio molitor* and *Tribolium confusum* were found to have an absolute requirement for niacin, even when grown in the presence of excess tryptophan. The tryptophan-niacin transformation mechanism is thus wholly lacking in these or-

ganisms. They resemble in this respect the animal protozoan, *Tetrahymena geleii* (G. W. Kidder, V. C. Dewey, M. B. Andrews, and R. R. Kidder, *J. Nutrition* **37,** *521 (1949)*), and the common fruit fly, *Drosophila melanogaster* (*Nutrition Reviews* **6,** *233 (1948)*), both of which also require both tryptophan *and* niacin for growth.

Fraenkel and Stern varied the level of casein (at the expense of carbohydrate) from 5 to 100 per cent of the ration in the diet of these insects, and determined the niacin requirement for optimal growth and survival of the insect larvae at each level of protein. The niacin requirement increased regularly with increase of protein. Five per cent of protein was sufficient for optimum growth, and at this level, 4 to 8 μg. of niacin per gram of ration sufficed for optimum development. By contrast, with 50 per cent of casein, from 64 to 128 μg. of niacin were required. These differences are of such large magnitude as to leave no doubt of the validity of the result.

Except to suggest that the extra niacin is required at some point in the process of utilization of protein for energy, the authors do not speculate about the reasons for this enhanced requirement in the presence of high protein. From what is now known of intermediary metabolism, however, it is difficult to see why utilization of protein for energy should require amounts of niacin so greatly in excess of those required for similar utilization of carbohydrate. Alternative explanations thus may be required for the known facts. If a similar situation exists in higher animals, however, it may be that conversion of "protein-bound" tryptophan to niacin is not nearly so inefficient as has been indicated by previous comparisons of the excretion of niacin and niacin metabolites in animals fed equal levels of free and combined tryptophan.

NITROGEN-SPARING EFFECT OF CARBOHYDRATE

Dietary carbohydrates have been known for some time to be involved in the economy of utilization of dietary nitrogen. P. S. Larson and I. L. Chaikoff (*J. Nutrition* **13,** *287 (1937)*) reported that the nitrogen-sparing effect of dietary carbohydrate was evident in adult dogs only if the protein and carbohydrate components of the diet were fed simultaneously or within four hours of each other. Similar results were reported by D. P. Cuthbertson, A. McCutcheon, and H. N. Munro for adult humans (*Biochem. J.* **34,** *1002 (1940)*) and by Munro for adult rats (*J. Nutrition* **39,** *375 (1949)*).

The mode of nitrogen sparing by carbohydrate has not been explained. In normal adult animals this sparing action is apparently transitory. The effect has usually been demonstrated only during the first few days, and after that time the nitrogen balance returns to its original values. E. Geiger (*Science* **108,** *42 (1948)*) considered it conceivable that the nitrogen-sparing action of sugar in the adult well-fed animal was probably transitory because the adult animal's ability to store protein is only transitory. In growing animals, where the dietary nitrogen could be used for the synthesis of new tissue, the simultaneous feeding of sugar and protein was found to improve the growth rate of young rats. In a more recent study (Geiger, R. W. Bancroft, and E. B. Hagerty, *J. Nutrition* **42,** *577 (1950)*) the nitrogen-sparing action of carbohydrate was reported in protein-depleted adult rats.

The basal food mixture used was composed of cornstarch, 51.6; Woodflock (powdered wood), 14.4; cod liver oil, 14.6; wheat germ oil, 4; and salt mixture, 15.4 per cent; and was fortified with the known vitamins. The basal mixture was fed at a

level of 2 g. per rat daily. Each rat also received daily 2.8 g. of butter, 4 g. of glucose and 2.5 g. of casein.

In the first experiment, 3 protein-depleted rats were fed the casein and glucose components of the diet separately (glucose at 9 a.m., and casein at 4 p.m.). Three similarly depleted animals received both the glucose and casein components of the diet at 4 p.m. All animals received the butter and basal mixture in the morning feeding. Food intakes were kept equal and the nitrogen intake was approximately 337 mg. per rat daily.

The simultaneous feeding of casein with glucose in all cases resulted in improved nitrogen retention. These animals retained an average of 923 mg. of nitrogen over a twelve-day experimental period, compared to an average retention of only 508 mg. in the animals receiving the casein separately as an afternoon meal.

The animals receiving the glucose and casein components of the diet simultaneously regained their original body weight in twelve days, at which time those receiving these dietary components separately had recovered an average of only 38 g. of the 52 g. of body weight lost during protein depletion.

In a second experiment, protein-depleted rats regained an average of only 12.3 g. of body weight in fourteen days when the glucose and protein components were fed separately, whereas those receiving glucose and protein simultaneously gained 46.6 g. during the same period.

In additional experiments alternate periods of separate and simultaneous feeding of glucose and protein clearly demonstrated the improved nitrogen retention resulting from the simultaneous feeding of these dietary components.

All of these studies indicate that the nitrogen-sparing effect of glucose is not transitory and that it actually persists for periods up to fifteen days, or until protein depletion has been corrected, as evidenced by return to normal body weight.

Geiger and associates have no explanation for the nitrogen-sparing action of sugar. They consider it conceivable, however, that the carbohydrates arriving at the liver via the portal circulation may have some specific physiologic function (acetylation or phosphorylation) which expedites the utilization of dietary amino acids. Support for such a theory is evident in the recent results reported by L. L. Miller, C. G. Bly, M. L. Watson, and W. F. Bale (*Fed. Proc.* **9,** *206 (1950)*. These workers noted that glucose enhanced the *in vitro* synthesis of blood proteins from amino acids in the isolated surviving liver of the rat.

Whatever the explanation, the results again emphasize that the supply of nutrients essential to good nutrition appear to be most efficiently utilized when fed together, as has already been demonstrated for the essential amino acids (*Nutrition Reviews* **5,** *316 (1947)*).

BODY FAT IN MAN

The amount of "excess" fat is one of the most variable characteristics of the human and animal body. It is closely related to the level of caloric intake and, in fact, may serve as the best single criterion of calorie nutriture. Illustrative data may be taken from C. R. Moulton's study (*J. Biol. Chem.* **43,** *67 (1920)*) on beef steers maintained for eleven months on calorie intake adequate for normal growth. On extraction, the carcass of the control animal, killed at that time, contained 18.5 per cent of fat. One of the experimental animals was full-fed for ten months and became "very fat," with

32.6 per cent of the body constituted by fat. Another steer was fed a restricted ration so that he lost about one-half pound of body weight per day and became "very emaciated." The fat content of the body was only 1.9 per cent.

A marked decrease or virtual disappearance of fat depots has been repeatedly noted in autopsies of famine victims. In grossly overnourished (obese) persons the fat depots are strikingly enlarged. During autopsy these deposits of adipose tissue may be separated from the other tissue and weighed. The practical limitations of the anatomical method are no less severe than the limitations of the chemical methods based on solvent extraction of fat. The unique, thorough biochemical analysis of one body (male, 35 years old) by H. H. Mitchell, T. S. Hamilton, F. R. Steggerda, and H. W. Bean (*J. Biol. Chem.* **158,** *625* (*1945*)) should be noted. The extractable fat represented 12.5 per cent of the total body weight.

The methods available for a quantitative evaluation of fatness-leanness, with emphasis on technics applicable to men, were reviewed by J. Brozek and A. Keys (*Nutrition Abstr. Rev.* **20,** *247* (*1950/51*)). The most promising indirect method involves measurement of the thickness of the skinfolds (subcutaneous tissue plus skin). There are three other technics which should be noted but which are restricted in their usefulness for purposes of nutritional investigations: determination of the thickness of subcutaneous tissues (plus skin) from x-ray photographs, estimation of the total excess fat from the specific gravity of the body, and estimation of body fat from the body water content.

N. B. Talbot (*Am. J. Dis. Child.* **55,** *42* (*1938*)) considered the creatinine coefficient, obtained as the ratio of creatinine excretion (in mg.) per twenty-four hours to the body weight (in kg.), as an index of relative obesity. However, even within the normal range of variation of body fat its value is questionable. There is little association between breadth of the fat layer of the calf and creatinine (E. L. Reynolds and L. C. Clark, *Child Development* **18,** *155* (*1947*)). In marked undernutrition associated with large losses of body fat, the creatinine coefficient fails completely. Instead of rising, as might be expected in view of marked fat loss, the creatinine coefficient decreased from 23.0 to 20.8 after twelve weeks of semistarvation, and to 18.8 after an additional twelve weeks (A. Keys *et al.*, "The Biology of Human Starvation," *Univ. of Minnesota Press, Minneapolis* (*1950*).

For purposes of nutritional surveys, the measurement of the thickness of the skinfolds is likely to be the most useful technic while the specific gravity method can be used to advantage for laboratory investigations. The x-ray technic has been applied for survey studies of nutritional status, *e.g.*, by H. C. Stuart and D. Kuhlmann (*J. Pediatrics* **20,** *424* (*1942*)), but the need for x-ray equipment and the cost make its widespread use prohibitive.

The human skin proper is thin and relatively uniform in thickness. D. A. W. Edwards (*Clin. Sci.* **9,** *259* (*1950*)) showed on the basis of measurements in 8 female cadavers that the average thickness of the double skin measured at 53 points varied between 1 and 4 mm., with an average of 2.2 mm.; the value exceeded 3 mm. in less than 10 per cent of the locations. The marked variation in the thickness of the skinfolds (in Edwards' study, 5 to 39 mm.), obtained by lifting the "skin" at different points of the body surface, is due to the differences in the layer of subcutaneous fat tissue. This fact makes possible the use of skinfolds as measures of fatness. A clinical evaluation of the amount of subcutaneous tissue has been used in some nutrition surveys (*e.g.*, J. B. Youmans, E. W. Patton, and R. Kern, *Am. J. Pub. Health* **33,** *58* (*1943*)). Quantitative determinations have been made by H. H. Mitchell (*Human Biol.* **4,** *469*

(*1932*)) in a study of nutriture of children in Puerto Rico and are currently used by the Oxford Survey Team; only fragmentary data are available at present. Norms for skinfolds below the scapula and above the ilium in boys and girls up to the age of 18 years were presented by H. V. Meredith and H. C. Stuart (*Am. J. Pub. Health* **37,** *1435* (*1947*)).

The density of body fat is considerably lower than the density of the other tissues. For guinea pigs, M. F. Morales, E. N. Rathbun, R. E. Smith, and N. Pace (*J. Biol. Chem.* **158,** *677* (*1945*)) give the values of 0.912 for fat, 1.066 for muscles, 1.43 for the wet skeleton. The low density of the fat makes possible the estimation of the fat content from the specific gravity (A. R. Behnke, *Harvey Lectures* **37,** *198* (*1941/42*)). In man the body volume, needed in the calculation of specific gravity, may be obtained as the difference between the body weight in the air and when fully submersed in water. The amount of air in the lungs during submersion must be taken into account (J. Brozek, A. Henschel, and A. Keys, *J. Applied Physiol.* **2,** *240* (*1949*)). The technic has been used in studying the effects of prolonged undernutrition (Keys *et al.*, *loc. cit.*) and of the rice-fruit diet (C. B. Chapman, T. Gibbons, and Henschel, *New Engl. J. Med.* **243,** *899* (*1950*)).

N. Pace and E. N. Rathbun (*J. Biol. Chem.* **158,** *685* (*1945*)) showed that it is feasible to estimate the amount of total fat not only on the basis of the specific gravity but also from the water content of the body, the lean (fat-free) body mass having a highly constant water content (in guinea pigs 72.4 per cent ±2.1 per cent). The methods for determination of total body water were reviewed by M. F. Levitt and M. Gaudino (*Am. J. Med.* **9,** *208* (*1950*)). Using antipyrine W. J. Messinger and J. M. Steele (*Proc. Soc. Exp. Biol. Med.* **70,** *316* (*1949*)) obtained a satisfactory correspondence between body fat estimated from total body water and from specific gravity in 9 individuals. Extensive data confirming this finding were reported by E. F. Osserman, G. C. Pitts, W. C. Welham, and A. R. Behnke (*J. Applied Physiol.* **2,** *633* (*1950*)). The technic appears to be too cumbersome for use in nutritional research.

In the past, the principal criterion for characterizing the degree of relative obesity was the tabular "standard" weight, obtained as the mean value for individuals of a given sex, age, and height. It is obvious that in different individuals the departure from a standard reference weight may result from a relative disproportion of the mass of several body components—muscles, adipose tissues, bones, and, in patients with edema, the extracellular fluid. W. C. Welham and A. R. Behnke (*J. Am. Med. Assn.* **118,** *498* (*1942*)) showed that identification of "overweight" with "obesity" may lead to grossly erroneous conclusions. The body weight of their group of professional football players was 25 per cent above the army standards, yet the men were actually "thin," *i.e.*, had low fat content.

The limitations of "normal" body weight as a criterion of normality, especially as far as the composition of the body is concerned, become readily apparent when one considers individuals of standard weight but differing in age (J. Brozek and A. Keys, *Science* **112,** *788* (*1950*)). To study the effects of ageing, 2 groups of healthy men were compared, obtained by selecting from a larger sample those individuals whose body weight was within ±5 per cent of the standard reference weight. In both groups the mean body weight coincided with the standard weight yet the older men (N = 66, mean age 49.1 years) had considerably larger depots of subcutaneous fat than the younger men (N = 37, mean age 22.1 years). The mean thickness of the skinfolds measured at abdomen, chest, back, arm and thigh were 25.3, 25.4, 20.3, 14.3 and 10.2 mm. in older men, and 13.7, 11.4, 11.7, 10.4 and 8.1 mm. in

the younger men. The specific gravity was also determined. Using the average correction values for the volume of residual air of 2.2 liters and 1.5 liters, the mean specific gravity of the two groups was 1.056 and 1.079, corresponding to 21.0 and 9.8 per cent of the body weight as fat. The values of residual volume were determined out of water. In the older men a value of 2.0 liters would probably have been closer to the true average value of residual volume at the time of submersion. Had this value been used, the difference between the younger and older men would have been still more striking.

Similar differences in fatness are observed if one compares men and women, the latter exhibiting a greater fat content. In middle-aged men the *tela subcutanea* alone constitutes about 10 per cent, in women about 20 per cent of the body weight (R. E. Scammon, in "Morris' Human Anatomy," *Blakiston, Philadelphia (1942)*). The literature on sex differences in fat content was reviewed (A. Keys *et al., op. cit., p. 171*). Additional recent evidence was provided by E. L. Reynolds and P. Grote (*Anat. Record* **102,** *45 (1948)*) who made measurements of the breadth of "fat" (skin plus *tela subcutanea*), muscle, and bone, using anterio-posterior roentgenograms of the calf at the position of greatest breadth, at seven age levels, up to early adult age (31 years). On the average, in the young adult woman the combined (medial and lateral) breadth of fat in the leg is about twice as great as in the young adult man, with the mean values of 19.7 and 9.6 mm. The sex differences were brought out even more strikingly in a later study in which E. L. Reynolds (*Human Biol.* **21,** *199 (1949)*) used the fat/bone index, obtained as the percentage ratio of fat breadth (combined medial and lateral thickness) to bone breadth (thickness of tibia plus fibula at the same level). For women (mean age 33 years) the mean value was 61.1, for men (mean age 38 years) 27.8.

In a sample of 100 men and 100 women, with a mean age of 37.8 and 38.0 years, respectively, E. L. Reynolds and T. Asakawa (*Am. J. Phys. Anthropol.* **8,** *343 (1950)*) reported the mean breadths of the fat layer, in mm., as 10.8 and 20.5 while the fat/bone index values were 27.6 and 62.2. The women had a considerably greater spread in the fat values, whether the fat layer was expressed as absolute tissue breadth, as percentage of the total breadth of calf, or as the fat/bone index. The standard deviations for the latter criterion were 9.6 for men and 19.9 for women.

The use of any measure of fatness for evaluation of an important aspect of the calorie nutriture of an individual presupposes the establishment of appropriate norms. It is apparent that such norms must be worked out for relatively narrow segments of the population, differentiated along the lines of sex, age, and most likely other criteria (*e.g.*, occupational activity and geographical location).

THE COMPOSITION OF ENAMEL AND DENTIN

Students of the oral tissues have long debated the question of whether or not the enamel and dentin could be considered to be vital structures. The discussion has been particularly keen with respect to the enamel, the hardest and densest tissue in the animal body. One reason for the controversy over the vitality of enamel has been the inability to demonstrate any pathways through which nutrients or waste products could pass. As recently as 1931, most interested dental investigators considered that there was insufficient evidence to demonstrate any phase of metabolic activity in mature enamel. One of the strong proponents of this view was S. W. Chase

(*J. Am. Dent. Assn.* **18,** *697* (*1931*)). He pointed out that there had been no demonstration that enamel could metabolize, grow, repair itself, reproduce, contract, respire or react to irritating stimuli. Hence mature enamel could not be vital. The inference was that the degree of calcification was so great as to reduce the organic components to insignificance.

In recent years through the application of precise, high-pressure and low-temperature decalcification procedures which prevent the formation of gas bubbles, the delicate, filamentous organic matrix has been freed of its complement of inorganic salts (*Nutrition Reviews* **6,** *70* (*1948*)). The preservation and visualization of the organic matrix has made possible a number of advances in our knowledge of dental structures. A number of landmarks, such as the striae of Retzius and the birth or neonatal line, which had previously been attributed to calcification variations during the development of the enamel, have been clearly demonstrated to be structural variations within the organic matrix (R. F. Sognnaes, *J. Dent. Res.* **28,** *549*, *558* (*1949*)).

Further studies of the dental tissues have been made through the use of a variety of histochemical staining technics. Some of these can be applied directly to the organic matrix which is liberated in the decalcification process. However, the use of mineral acids to demineralize the teeth alters the nature of a number of the organic constituents. Hence, a number of the histochemical procedures must be applied to ground sections. The latter technic is fraught with difficulties because of the problems encountered in preparing sufficiently thin ground sections and because the highly calcified structures have an extremely low permeability to staining reagents.

The first extensive use of histochemical reactions for the study of the natural components in teeth was reported by G. B. Wislocki, M. Singer, and C. M. Waldo (*Anat. Record* **101,** *487* (*1948*)). The dentin and pulp were most extensively studied in this work. The dentin is composed of three major entities: Tomes' fibers which are processes of the dentin-forming cells (odontoblasts), the sheath of Neumann which encircles Tomes' fibers throughout their entire length, and the ground substance which occupies the rest of the dentin. Tomes' fibers run a reasonably straight course parallel to each other from the pulp to the junction of the dentin with the enamel. These fibers have often been spoken of as pathways through which impulses, nutrients and by-products might pass. Tomes' fibers stain black with Sudan Black B which suggests the presence of phospholipids, react positively with the periodic-acid Schiff technic, stain with acid dyes, and are variably impregnated by Pap's ammoniacal silver method. The sheaths of Neumann exhibit all the staining reactions which are characteristic of acid mucopolysaccharides. The protein in the ground substance gives all the reactions representative of collagen. The ground substance of the pulp of monkey and human teeth gives faint reactions for acid mucopolysaccharides. In contrast, the ground substance of the pulp of guinea pig molars which grow and erupt continually is much more metachromatic, indicating a higher concentration of acid mucopolysaccharides. The latter finding is not unexpected in view of the appreciably greater rate of growth in the guinea pig teeth.

This type of investigation has been continued and extended, with particular reference to the enamel, by G. B. Wislocki and R. F. Sognnaes (*Am. J. Anat.* **87,** *239* (*1950*)). In enamel, there is also evidence of a marked metachromasia throughout the organic matrix which is indicative of the presence of an acid mucopolysaccharide. Part of the basophilia may be due to one stage in the process of keratinization. Reactions for alkaline phosphatase and lipids occur in the organic sheaths around the calcified prisms. The organic matrix gives

the Prussian blue reaction for sulfhydryl groups as well as other staining reactions indicative of keratin. In this way, the protein of the organic matrix is typical of the protein of other tissues which originate from the ectodermal layer of germ plasm. Thus, even though enamel is very highly calcified and extremely dense, the organic components thereof can be characterized in terms of entities which occur elsewhere in the body.

In another investigation, R. F. Sognnaes and G. B. Wislocki (*Oral Surg. Oral Med. Oral Path.* **3,** *1283 (1950)*) reported their observations obtained with histochemical studies of carious teeth. Tooth decay in the enamel seems to be initiated by demineralization and depolymerization of the acid mucopolysaccharide which is normally present in the organic matter between the enamel prisms. Demineralized enamel gave reactions for sulfhydryl groups, keratin, and lipids. The lipid reaction seems to be largely due to the invading microorganisms. Caries of the dentin appears to be initiated by demineralization and a change in the acid mucopolysaccharides in the walls of the dentinal tubules (Neumann's sheaths). Apart from the changes in the acid mucopolysaccharide the dentinal tubules in early caries were not swollen and did not appear to have been invaded by any microorganisms which could be detected by routine bacterial staining technics. No alkaline phosphatase was demonstrated in carious lesions of human teeth but variable amounts were detected in the lesions experimentally produced in rat molars.

The presence of enzymes, acid mucopolysaccharides, lipids, etc., in the highly calcified tissues of the teeth suggests that these tissues have heretofore unrecognized potentials for metabolic activity. These studies coupled with radioisotope investigations such as those of R. F. Sognnaes, J. H. Shaw, A. K. Solomon, and E. Harvold (*Anat. Record* **104,** *319 (1949)*) point out the need for continued emphasis upon these phases. The radioautographs in the latter paper present in striking fashion a rough estimate of the rate of turnover of phosphorus during normal metabolism. Particularly fruitful fields for investigation lie in the production of a variety of nutritional deficiencies in experimental animals during periods of tooth development to see if the distribution of these organic components may be altered and to determine if teeth formed during deficiency states may have altered abilities to metabolize. The ultimate solution of the seemingly enigmatic problem of tooth decay may well be the outcome of the combined results of such studies.

CHOLINE DEFICIENCY IN THE CALF

Choline has been shown to be a dietary essential for several species of animals and recent studies indicate that the dietary requirement of choline for the newborn pig is exceedingly high.

B. C. Johnson, H. H. Mitchell, J. A. Pinkos, and C. C. Morrill (*J. Nutrition* **43,** *37 (1951)*) have recently studied choline deficiency in newborn calves. Ten one- to two-day-old calves were fed a "synthetic milk" diet consisting of casein (15 per cent) cerelose (52 per cent), lard (27 per cent), minerals (6 per cent), nine B vitamins and four fat-soluble vitamins. Three calves received this diet supplemented with 200 mg. of choline chloride per 100 g. dry matter of the diet. The other 7 calves received only the unsupplemented basal diet.

The calves receiving choline gained rather poorly during the first month of life but did survive and gained an average of 0.35 pounds per day. The 7 calves fed the choline-free diet failed to gain weight, ate poorly and became moribund in approximately seven days. The symptoms included marked weakness, inability to walk, labored

or rapid breathing, and anorexia. Four calves died and pathologic examination revealed renal hemorrhages in 2, and slight fatty infiltration of the liver in 3. The intravenous or subcutaneous administration of one gram of choline to each of the other 3 calves resulted in dramatic improvement. Within twenty-four to forty-eight hours after administration of choline the strength of the animals was regained and their appetites improved.

Hematologic studies revealed a slight anemia in only 2 of the animals. The total leukocyte count was essentially unaltered although with one exception the calves fed the choline-free diet showed a higher percentage of lymphocytes than did the calves on the choline-containing diet. The level of choline in the urine of the calves on the deficient diet was considerably reduced.

The removal of choline from the diet of 3 calves after they had received the original therapy was without demonstrable clinical or pathologic effects.

From these experiments it would seem that choline is a very critical dietary essential in the newborn calf. It is surprising that a fatal deficiency resulted so rapidly, especially since the calves received colostrum from the cows for one to six days. R. K. Waugh, S. M. Hauge, and W. A. King (*J. Dairy Sci.* **30,** *457 (1947)*) have shown that colostrum is a good dietary source of choline. Thus it seems that the dietary requirement for choline is considerably greater during the first week or two of life than later.

PLASMA ALKALINE PHOSPHATASE

Measurements of alkaline phosphatase in the circulating blood have been of interest to nutritionists for many years, primarily as an indication of nutriture with respect to calcium and vitamin D (*Nutrition Reviews* **2,** *331 (1944)*). In contrast to the low concentrations observed in normal adults, higher values are found in children, with peaks in early infancy and during adolescence. Alkaline phosphatase is widely regarded as a measure of osteoblastic activity. An association between alkaline phosphatase activity and the hormonal changes associated with growth has been an attractive hypothesis.

Measurements of plasma alkaline phosphatase in a large group of normal infants and children observed over a period of years at the Fels Research Institute have been reported by L. C. Clark and E. Beck (*J. Pediatrics* **36,** *335 (1950)*). The micromethod of O. A. Bessey, O. H. Lowry, and M. J. Brock (*Nutrition Reviews* **5,** *71 (1947)*) was employed. Nitrophenylphosphate is the substrate used in this method. The amount of nitrophenol liberated under the specified conditions is measured. The results are expressed in nitrophenol units which are equivalent to 1.79 Bodansky units.

Over 1000 determinations were made on a group of normal infants, children, and young adults over a three-year period. Examination of the year-to-year correlations revealed that a given child tends to stay at a particular level. When the data are tabulated according to age and sex groups certain well-defined trends become apparent despite a very wide range of values in each age group. During the first year of life the values ranged from 5.13 to 12.60 units with a mean of 8.22 units. During the years from 2 through 12 a plateau was reached. Determinations varied from 1.81 to 11.48 units and the mean values fell between 5.93 and 6.67 units. No sex differences were apparent in the children.

The values for girls fell during the 12- to 18-year period and attained an adult value of approximately 2 units. For the boys in

the 13-year-old group there was slight rise to 7.26 units from the childhood plateau with values ranging from 3.79 to 14.0 units. This was followed by a fall which was at first sharp, then gradual after the age of 17, reaching adult values early in the third decade of life. Single determinations greater than 4.5 units were not found in subjects over 17 years of age. The difference between the sexes first became apparent during puberty and diminished by the age of 21.

The origin of the plasma alkaline phosphatase in normal children is not exactly known. The alkaline phosphatase activity of extracts of bone and kidney is inhibited by 50 per cent in the presence of taurocholate while the activity of intestinal extracts is not (O. Bodansky, *J. Biol. Chem.* **118,** *341 (1937)*). These findings have been confirmed by the present authors. Consequently the fact that plasma alkaline phosphatase activity was inhibited by 50 per cent in the presence of taurocholate would suggest that it is largely derived from either kidney or bone. When normative data for the rate of bone growth as indicated by height measurement (L. W. Sontag and E. L. Reynolds, *J. Pediatrics* **26,** *327 (1945)*) were compared with plasma alkaline phosphatase activity a parallelism became apparent. This observation would support the hypothesis that the bones were a major source of the plasma activity.

Comparable findings from nutrition surveys of two large groups of school children have been reported (O. A. Bessey and O. H. Lowry, "Nutritional Assay of 1200 New York State School Children," *Public Health Research Institute of the City of New York (1948)*; A. P. Harrison *et al.*, *J. Am. Dietet. Assn.* **24,** *503 (1948)*). The trends for groups separated on the basis of age and sex are similar. Although it has been suggested (Bessey and Lowry, *loc. cit.*) that values greater than 8 nitrophenol units are indicative of poor nutrition, neither Harrison and co-workers nor the present authors have found either clinical or roentgenologic evidence to support this point of view. The limits of normal for any particular age and sex have not yet been sharply defined.

Interpretation of the nutritional significance of determinations of plasma alkaline phosphatase activity will be aided by wider appreciation of the variability between individuals and of the trends associated with growth and maturation.

THE B VITAMINS AND TRYPTOPHAN METABOLISM

Once the observation was made that tryptophan is intimately associated with the synthesis of niacin, the metabolic pathway whereby this transformation occurs was worked out with a fair degree of accuracy; there is convincing experimental evidence that kynurenine and 3-hydroxyanthranilic acid are prominent intermediates in this biologic process. That other vitamins play a part in facilitating the synthesis of niacin from tryptophan might be expected and it was soon shown that pyridoxine deficiency in rats was followed by the appearance in the urine of abnormal amounts of certain metabolites after the administration of tryptophan, notably the increased excretion of xanthurenic acid (E. C. Miller and C. A. Baumann, *J. Biol. Chem.* **159,** *173 (1945)*). Furthermore, after tryptophan is given the normally-appearing derivatives of niacin in the urine are reduced in vitamin B_6-deficient animals (C. T. Ling, D. M. Hegsted, and F. J. Stare, *Ibid.* **174,** *803 (1948)*). Similar observations have been made in rats when thiamine, riboflavin or folacin has been lacking in the diet (P. B. Junqueira and B. S. Schweigert, *Ibid.* **175,** *535 (1948)*; C. C. Porter, I. Clark, and R. H. Silber, *Arch. Biochem.* **18,** *339 (1948)*).

In view of the foregoing data, a study (L. M. Henderson, I. M. Weinstock, and G. B. Ramasarma, *J. Biol. Chem.* **189,** *19 (1951)*) has been reported which was designed to elicit information regarding the site of action of the B vitamins in the metabolic pathway of tryptophan. Inasmuch as tryptophan, kynurenine and 3-hydroxyanthranilic acid are apparently metabolized in the same pattern and apparently in the sequence given, a method is presented for determining the stage in the metabolic transformation at which the B vitamins exert their influence. The criterion of abnormality was the comparative urinary excretion of quinolinic acid in rats given an adequate control diet and in those on a vitamin-deficient diet. The experimental rations contained either 9 or 18 per cent casein with crystalline B vitamins added separately so that the one being studied could readily be omitted. When the signs of deficiency became severe, as shown by cessation of growth, tryptophan, DL-kynurenine sulfate or 3-hydroxyanthranilic acid was given by stomach tube or (in later experiments) by intraperitoneal injection. Urine was collected for forty-eight hours before, and for the same period after the administration of the test substances.

In the experiments on pyridoxine deficiency, the excretion of quinolinic acid in the urine was greatly decreased when either tryptophan or kynurenine was given, but was in the range of the amount excreted by the control rats when 3-hydroxyanthranilic acid was administered. This indicates that the point of action of pyridoxine is subsequent to both tryptophan and kynurenine but prior to the 3-hydroxyanthranilic acid stage. This conclusion was again clearly supported when the vitamin B_6-deficiency was produced by feeding the antivitamin desoxypyridoxine. When riboflavin deficiency was studied there was again a clear interference with the metabolic progress of tryptophan and of kynurenine, whereas 3-hydroxyanthranilic acid was converted to quinolinic acid as well as in the control animals. The factor of inanition, as brought out through the use of pair-fed controls, appears to have played too large a part to warrant an interpretation of the results when thiamine-deficient rats were studied.

From the foregoing most recent observations it appears that the step between kynurenine and 3-hydroxyanthranilic acid is most susceptible to the metabolic disturbance occasioned by the lack of pyridoxine and riboflavin. In view of the evidence (Porter, Clark, and Silber, *loc. cit.*) that riboflavin exerts little influence on kynurenine or xanthurenic acid excretion after tryptophan administration, the suggestion is made that this vitamin affects the metabolic process somewhat earlier, *i.e.*, prior to 3-hydroxykynurenine, and that pyridoxine plays its part subsequent to the 3-hydroxykynurenine stage.

OCCUPATIONS AND CALORIE NEEDS

Recent detailed considerations of calorie requirements (*F.A.O. Nutritional Studies No. 5 (1950); cf. Nutrition Reviews* **9,** *40 (1951)*) have been focussed on the needs of the total population of a country, the extrapolations from a reference scale taking into account adult weight, environmental temperature, age and sex composition of the population. The occupational activity of the reference man and the reference woman were considered as corresponding to energy output of workers engaged in light to moderately heavy work, with a mean daily calorie requirement, on a year-round basis, of 3200 and 2300 calories. However, occupational activity, although admittedly directly influencing calorie requirements, was not specifically considered, on the grounds that in

most populations the mean activity will approximate the degree of activity assigned to reference adults. The lack of adequate and realistic research data on the actual caloric cost of occupational work, the variability in energy expenditure within groups of operations carrying the same occupational label, and the fact that nonoccupational activity is more important than is commonly indicated in the textbook tables of calorie requirements of people engaged in particular occupations may have contributed to the disinclination of the FAO Committee on Calorie Requirements to enter upon the discussion of this matter.

The Technical Commission of the League of Nations in its "Report on the Physiological Bases of Nutrition" ("The Problem of Nutrition," *Vol. 2, League of Nations Official Publication No. A. 12(a)(1936)II B*) set calorie supplements for muscular activity at levels of up to 75 calories per hour of light work, 75 to 150 for moderate work, 150 to 300 for hard work, and 300 and over for very hard work. The recommendations of the daily calorie allowances made by the National Research Council (*Reprint and Circular Series No. 129, Washington (1948)*) distinguished three levels of activity, without detailed specifications. The daily intakes for sedentary, moderately active, and very active women were given as 2000, 2400, and 3000 calories respectively; for men who are sedentary, physically active, and doing heavy work as 2400, 3000, and 4500 calories. The values for the first two categories of man's work are very close to Rubner's standards for light and medium-heavy activity; these values, dating to 1903, as well as the results of the early investigations carried out by Voit, Atwater, Carpenter and others are cited by G. Lusk ("The Elements of the Science of Nutrition," *3rd ed., W. B. Saunders, Philadelphia (1919)*).

What is the typical textbook information on calorie requirement for various types of activity? E. E. Hawley and E. E. Maurer-Mast ("The Fundamentals of Nutrition," *(p. 47) C. C. Thomas, Springfield, Ill. (1940)*) reprinted a table derived from the ancient experiments by Atwater and Benedict. It contains some remarkably detailed information, such as the hourly energy expenditure while knitting 23 stitches per minute, but the table provides little or no guidance to the contemporary world of occupational activities in which "shoemaking" has largely perished as a unitary occupational activity. The two brief tables, reprinted from Tigerstedt (source not cited), indicate that the energy demands in the same work category vary, with a range of 300 calories for a weaver and 900 calories for a farm laborer, but the details needed for a practical extrapolation are absent.

J. S. McLester ("Nutrition and Diet in Health and Disease," *4th ed., W. B. Saunders, Philadelphia (1943)*) relies heavily on the comprehensive review of man's energy requirements prepared by J. B. Orr and I. Leitch (*Nutrition Abstr. Rev.* **7,** *509 (1938)*). Included also is a table of daily total energy requirements, based on eight hours of occupational work, estimated by G. Becker and J. W. Hämäläinen (*Skand. Arch. Physiol.* **31,** *198 (1914)*) for 8 male and 5 female occupations. This table has been reprinted from McLester by E. F. Du Bois and W. H. Chambers in Chapt. IV of the American Medical Association's "Handbook of Nutrition" (*Chicago (1943)*). Because of the halo of authority of the Handbook, one finds the same material on energy requirements cited in such recent textbooks as Sarah R. Riedman's "The Physiology of Work and Play" (*Dryden Press, New York (1950)*). In the process of repeated second-hand citations, the fact that the initial values were obtained almost half a century ago has long been lost from sight.

The effect of muscular activity on the calorie requirement of adult man was discussed by A. Keys (*Nutrition Abstr. Rev.* **19,** *1 (1949)*), but the activity factor was given less prominence than body size, age, and climate. Several considerations were of-

fered to justify the skeptical attitude towards the validity and practical value of including occupational activity in the factorial (summation) system of calculating the total calorie expenditure. The paucity of experimental data and the limited number of activities studied in a few experimental subjects were considered as the most decisive obstacles. There were other objections as well. In many of the investigations the energy expenditure was determined during the active pursuit of the particular activity—while the carpenter was busy hammering, the painter plying his brush, etc. Multiplication of the values obtained during such bouts of activity, extending over a period of time measured in minutes, by a time factor to get an eight-hour day would yield gross overestimates of the energy expenditure for all but the most sedentary occupations. In the early studies carried out by F. W. Taylor at the Bethlehem Steel Co. ("The Principles of Scientific Management," *Harper, New York (1916)*) the author estimated that in heavy muscular work, such as lifting and carrying pieces of pig iron weighing 92 pounds each, a first-class workman can be under load only for 43 per cent of the time, but must be entirely free from load the remaining 57 per cent of the work day if he is to maintain his work capacity.

Another point criticized by Keys (*op. cit.*) is the customary procedure, in adding up the calories expended for different activities, to neglect the body weight, while in reality in numerous types of physical activity the movement of the body itself contributes significantly to the energy expenditure. Carrying sacks of flour or feed up a flight of stairs is a good example. Keys considers the failure to allow for body weight in such calculations as absurd as is the absence of an allowance for body size in the rationing systems.

One other point should be mentioned. In calculating the caloric requirements by the summation system, values are likely to be used which have been rendered obsolete by the rapid and sweeping changes wrought by modern technologic developments. There was a progressive reduction in the energy expenditure per hour of work, most of the industrial jobs now falling into the category of "moderate" work. The shortening of the total hours worked during a week reduces still further the fraction of the total energy expenditure accounted for by occupational activity.

The most comprehensive summary of the literature on energy expenditure in different occupations, available in English, has been made by Orr and Leitch (*loc. cit.*). The activities have been grouped under the categories of domestic and artistic occupations, industrial occupations, and physical exercise. At times even the original investigations do not provide the data needed for evaluation of the results, such as the number of subjects, duration of the work period studied, and other details needed for a practical application and extrapolation of the data. In spite of the limitations inherent in the available data, however, the authors believe that calorimetry, taken in conjunction with industrial time schedules, provides a method which may serve as a basis for arriving at reliable estimates of the calorie requirements of different industrial occupations.

By far the most extensive calorimetric research on energetic demands of occupational work has been undertaken by the Max Planck Institute for Work Physiology in Dortmund, Germany, and reported at length by G. Lehmann, E. A. Müller, and H. Spitzer (*Arbeitsphysiol.* **14,** *166 (1950)*). The study comprised 1800 determinations of energy expenditure, made on a total of 437 industrial workers and 167 different activities. The work was stimulated by the absence of valid standards for food rationing during the Second World War.

The caloric cost of work was determined at the actual work place, using Douglas bags for collecting the expired air, or the apparatus designed by E. Kofrányi and H. F. Michaelis (*Arbeitsphysiol.* **11,** *148 (1941)*). In the latter procedure the amount of the

expired air is determined by a gas meter and only a part of the air is collected for purposes of analysis.

Respiratory studies cannot be carried out over several hours, whether a mouthpiece or a mask is used for collecting the expired air. Consequently, proper sampling of work periods, during which energy expenditure is measured, becomes of utmost importance for the accuracy of arriving at the caloric equivalent of work expenditure during the whole shift. In occupations characterized by a highly uniform activity one may be satisfied with work periods of 10 to 15 minutes; knowing the duration of authorized and unauthorized rest pauses, it is possible to arrive at a fairly accurate estimate of the total caloric cost of work. This presupposes, however, that the intensity of the work is typical of the worker's daily output, a condition which must be checked in cooperation with the time-study and production engineers. In occupations which consist of a number of tasks, widely varying in their caloric demands, separate determinations must be made for the job components.

The results are given in 29 tables representing different groups of occupations, such as coal mining, steel mills, radio assembly, printing, shoemaking, saw mills, transport, and housework. What was the daily caloric expenditure in some of the jobs? In the printing industry the values were between 2500 and 2900 calories, radio repair averaged 2970, shoe repair and shoe manufacture (by hand) 3000 to 3100 calories, wood industry 3000 to 3300 calories (except for cutting firewood on a circular saw, 4100 calories), operation of presses in plastics industry, 3400 calories, locomotive engineers 3100 to 3500 calories and firemen 3500 to 4700 calories, stone cutting 3100 to 3800 calories, loading of stone 4300 calories, railroad bed repair 4800 calories. A few industrial jobs held by women were also investigated, with expenditure of 2500 calories in steel grinding, 2700 calories in placing bricks on carts, 2900 in carrying tile.

The treatment of the calorie demands in different industries gains in realism through a detailed discussion of the working conditions and a number of pictures of the actual places of work. In some instances, although altogether too few, the calculated caloric "requirements" were checked directly against actual caloric intakes. This could be done with considerable precision in instances in which the workers were living in special camps. For practical purposes this procedure is preferable whenever the caloric intake can be established with a tolerable accuracy; the food intake data must be supplemented by information on body weight observed over a period of weeks or months and data on the level of output. The studies of actual food consumption incorporate also the energy expenditure during nonoccupational activities which otherwise must be only estimated. The authors used the value of 250 calories as the caloric equivalent of nonoccupational work

Of some interest is a comparison of energy consumption estimates obtained on the basis of respiratory determinations and from food consumption studies made by H. Kraut and H. Bramsel (*Arbeitsphysiol.* **12,** *197 (1942)*), although the grouping of the occupations in these investigations is too broad and data on food consumption are available only for families, not for individual workers. Perhaps the most important conclusion to be drawn is the very serious limitation of the latter method. Thus the caloric expenditure of "metal workers," grouped by Kraut and Bramsel in one category with an intake level of 3150 to 3450 calories, varied on the basis of respiratory studies from 2700 to 4950 calories.

In the current usage, and in the German rationing system, some jobs have been regarded as "very hard work" because stressful environmental circumstances are a prominent feature of the job. Thus in highly mechanized rolling mills the work was actually light to moderately hard, with a caloric expenditure from 2700 to 3400 calories,

but it was done in extreme heat and was classified together with jobs granted the highest caloric ration supplement. Obviously, proper physiologic characterization of job demands is needed for a rational management of nutrition.

It would be technically impossible to study in detail all of the occupations in order to determine energy consumption. With the aim of increasing the accuracy of estimating the caloric expenditure of industrial workers on the basis of time-studies alone, the authors prepared a table indicating the calorie cost of position and locomotion (sitting or lying down, standing, walking, climbing) and of light to hard work involving the hands, arms, and the whole body. These values are added to the figure for basal metabolism (1680 calories for men, 1400 calories for women), cost of nonoccupational activities (250 calories), cost of digestion and specific dynamic action (6 per cent of the total), and a correction for incomplete utilization of food calories (6 per cent).

The study ends with a comprehensive table of estimated calorie requirements for 150 jobs in agriculture, industry, transportation and business. It incorporates empirical data obtained by Lehmann *et al.* and takes into account information provided by other investigators, particularly in indicating the range of the expected values. This table should replace the antiquated data frequently cited in nutritional textbooks.

STRAIN DIFFERENCES IN PROTEIN REQUIREMENT OF MICE

Considerable information has been accumulated on the nutritional requirements of experimental animals, such as the mouse and the rat. Very little information is available, however, on the nutritional requirements of inbred strains of such animals.

The nutritional requirements of the highly inbred strains of mice used extensively in experimental cancer studies have only very recently been investigated. P. F. Fenton and G. R. Cowgill (*J. Nutrition* **34,** *273 (1947)*) reported that strain C_{57} mice had a lower requirement for riboflavin than strain A mice. These strains differed markedly in their susceptibility to spontaneous mammary tumors, the A strain being susceptible and the C_{57} strain being resistant. Fenton, Cowgill, M. A. Stone, and D. H. Justice (*Ibid.* **42,** *257 (1950)*) also noted that strain C_{57} mice required less pantothenic acid for growth than did strain A mice, or mice of the C_3H strain, a strain highly susceptible to mammary tumors.

Recently P. F. Fenton and C. J. Carr have determined the protein requirements for growth in 4 inbred strains of mice (*J. Nutrition* **43,** *441 (1951)*). The strains studied were C_{57}, I, A, and C_3H. The I strain is similar to the C_{57} strain in that it is resistant to spontaneous tumors, whereas the A and C_3H strains have a high incidence of spontaneous tumors.

Three levels of dietary protein were tested, 10, 30, and 90 per cent. At the lower levels, vitamin-free casein served as the dietary protein whereas in the high protein diets lactalbumin, blood fibrin and egg albumin were also tested at 80 or 85 per cent levels in the presence of 10 or 5 per cent of casein. The diets contained 5 per cent of salt mixture, 5 per cent of corn oil, and dextrin or sucrose, where necessary, to equal 100 per cent. The diets were supplemented with the following (milligrams per 100 g. of diet): thiamine and pyridoxine, 1; riboflavin, 2; nicotinic acid, 5; pantothenic acid, 10; choline chloride, 150; biotin, 0.02; and folacin, 0.5. Fat soluble supplements included 1000 I. U. of vitamin A, 100 I. U. of vitamin D, 5 mg. of alpha-tocopherol and 1 mg. of 2 methyl-naphthoquinone per 100 g. of diet.

Mice of the 4 strains were weaned at 21 or 22 days of age and placed on the experimental diets. Food consumption and weight gains were recorded. Mice of the I and C_{57}

strains made relatively poor weight gains on the 10 per cent-protein diet. Over a thirty-day experimental period these strains increased their body weight approximately 6 g. In contrast, mice of the C_3H and A strains increased their body weight approximately 14 g. over a thirty-day period on the 10 per cent-protein diet. These differences were also evident when protein efficiency ratios were calculated for the first fifteen days. The grams of body weight gained per gram of protein consumed were 1.43, 1.13, 0.98, and 0.65 for strains C_3H, A, C_{57} and I respectively.

On the 30 per cent-casein diet the average thirty-day body weight gains were 14, 13, 12 and 10 g. respectively for strains C_3H, A, C_{57} and I. It is thus evident that increasing the dietary protein from 10 to 30 per cent had no influence on the growth rate of strains C_3H and A, but resulted in a marked increase in the growth rate of strains C_{57} and I.

When the diet containing 90 per cent as casein was fed, the mice of strains C_{57}, A, and C_3H behaved alike and all gained about 9 g. in body weight during the thirty-day period. Strain I mice, in contrast, gained only about 5 g. during the same period on this diet. The poorer gain of the strain I mice on the 90 per cent-casein diet was partially corrected by adding 3 per cent of sodium bicarbonate to the diet. When a diet containing 85 per cent of lactalbumin and 5 per cent of casein was fed to the mice of I strain, they made body weight gains equal to that observed with the 30 per cent-casein diet. Poor growth resulted when diets were fed that contained 85 per cent of egg albumin or blood fibrin.

These studies emphasize the fact that inbred strains of animals of a given species are characterized by different metabolic patterns which are reflected in differing nutrient requirements. The results clearly indicate that strain differences do exist with respect to the utilization of protein for growth in mice. In the strains studied it was apparent that those with the lower protein requirement were distinguished by their susceptibility to spontaneous tumor development, while the strains with a high protein requirement were resistant to tumors.

Summarizing these observations and those reported earlier by Fenton and associates, it would appear that the riboflavin and pantothenic acid requirements are low in strains which have a high protein requirement, and that such strains are further characterized by their resistance to spontaneous tumor development. The vastly different protein efficiency ratios which were observed on a 10 per cent-protein diet in the 4 strains of mice studied obviously indicate, as pointed out by the authors, that in reporting protein efficiency studies it is imperative that information be given on the strain of animal and the source of animals used for such studies.

These observations are of a great deal of interest, and further studies of this nature should help to clarify the genetic as well as the environmental factors (nutrition in particular) that are in some way determinants in the development of cancer. Fenton and his associates point out that a great many more studies of this type are necessary before it can be concluded that a given pattern of nutrient requirement can be relied upon as a criterion for assessing an animal's resistance or susceptibility to neoplastic growth.

SODIUM RESTRICTION IN CONTROL OF ASCITES

Cirrhosis of the liver of the nutritional or alcoholic type in man is frequently if not usually associated with changes in distribution of body fluids and the accumulation of

fluid within the abdomen and in tissues of the lower extremities. A number of factors have been implicated in the mechanisms responsible for the development of abdominal ascites in patients with cirrhosis (*Nutrition Reviews* **7,** *26, 345 (1949)*; **8,** *243 (1950)*).

The first of these is the mechanical factor of increased pressure within the portal venous system producing increased hydrostatic pressure and allowing for loss of fluid through the walls of blood vessels within the abdomen. Pressures increase due to fibrotic scarring in the areas about the portal spaces at the periphery of the liver lobules. In addition, the development of numerous arteriovenous intercommunications between the distal branches of the hepatic artery and the portal vein contributes to the increased pressure within the portal system. A second factor is that of decreased colloid osmotic pressure associated with decreased concentrations of plasma albumin in cirrhosis which permits transudation of fluid through capillary walls.

There is evidence as well that hormonal factors are involved in the production of ascites, since it has been demonstrated that patients with cirrhosis who also have ascites excrete in the urine increased quantities of antidiuretic hormone derived from the posterior pituitary. It is postulated that the increased urinary excretion of this hormone results from failure of the damaged liver to inactivate the hormone.

Finally, it has been shown that cirrhosis is accompanied by defects in the metabolism of electrolytes which facilitate the accumulation of intra-abdominal fluid. Particularly, it has been found that the cirrhotic patient with ascites retains sodium. The roles of the various known factors in production of ascites are considered and evaluated in a combined staff clinic of the College of Physicians and Surgeons of Columbia University which was published recently (*Am. J. Med.* **9,** *102 (1950)*).

It is the purpose of this review to consider the use of a low sodium diet in the management of ascites in the effort to combat the consequences of sodium retention and to control the accumulation of intra-abdominal fluid. This approach has been utilized and the clinical experience evaluated in a report by R. W. Phillips and A. M. Phillips (*Arch Int. Med.* **87,** *636 (1951)*). Five patients with portal cirrhosis and ascites were observed during periods with and without dietary restriction of salt. Each patient received a diet described as containing relatively large proportions of protein and carbohydrate but with limited content of fat. The character of the diet is not further described except to state that there was no effort to limit the quantity of salt consumed. After control periods of variable length on this diet, patients were given a special diet which provided 3400 calories, 135 g. protein and sodium restricted to 605 mg. daily. Throughout control periods and periods of sodium restriction the patients received supplementary vitamins, methionine and liver extract intramuscularly. Throughout the investigation of each patient body weight, fluid intake and output, and urinary excretion of chloride were determined daily. In addition, analyses of a number of blood constituents and tests of liver function were done at selected intervals.

Three of the five patients required removal of the ascitic fluid by paracentesis during periods on the control diet. Consumption of the low salt diet was initiated in each of these patients following paracentesis. Additional paracenteses were not needed in any patient following institution of dietary sodium restriction. Clinical observations indicated either resorption of the intra-abdominal fluid or persistence of lesser degrees of ascites. The two patients who did not require paracentesis prior to sodium restriction gained weight and accumulated ascites during the period of ingestion of the control diet but then lost weight with in-

creased urinary output and decrease in ascites. One patient was free of all evidence of ascites after thirty days on the low sodium diet, while the second had achieved this state after twenty-two days.

A patient who no longer had clinical manifestations of ascites or edema after about thirty-five days of salt restriction was then given the control diet and unlimited salt for eight days without reaccumulation of fluid. Two other patients were given 4 g. of sodium chloride daily as enteric coated tablets after control of ascites had been achieved on the low salt regimen. One of these rapidly gained weight and accumulated ascitic fluid. There was no increase in urinary chloride during the period of salt administration, indicating that the salt given was retained. The second patient responded to the salt supplement with increased urinary output and a marked rise in the urinary excretion of chloride. This result was taken as indicating that the patient had by salt restriction decreased his total body sodium so that fluid had accumulated in tissues and was mobilized by the salt supplements given. This contention might have been proven had the authors been able to include in their study determinations of serum and urinary sodium.

In all but one of the patients there was evidence of improvement of liver function as determined by the liver function tests done during the period of sodium restriction. It is perhaps unwarranted to indicate that these gains were the result of the low salt diet. It should be pointed out that the diet contained large quantities of protein and were supplemented with vitamins, methionine and liver extract, providing the type of diet which is of established importance in the therapy of primary disorders of the liver.

The report of Phillips and Phillips (*loc. cit.*) is of importance because it substantiates the earlier therapeutic claims of other investigators who were able to study in somewhat more detail the electrolyte imbalance associated with formation of ascites. W. J. Eisenmenger, E. H. Ahrens, S. H. Blondheim, and H. G. Kunkel (*J. Lab. Clin. Med.* **34,** *1029 (1949)*) limited the sodium chloride intake of 13 patients with ascites accompanying cirrhosis to less than 1.0 g. per day. Twelve of the 13 patients ceased accumulation of ascites on this dietary regimen. The urinary output of each patient increased as fluid was mobilized. After three months of salt restriction the patients were provided salt in quantities usually consumed in the normal diet. Four patients did not redevelop ascites, whereas eight patients did again accumulate fluid intra-abdominally. These investigators found that sodium chloride excretion remained very low despite variations in intake of sodium chloride in patients with ascites and that the intake of salt must be reduced to less than 1.2 g. per day if ascites formation is to be controlled. They also observed that concentrations of serum protein increased during consumption of diets containing little salt. This was thought to be the result of avoidance of loss of protein in ascitic fluid which earlier had been removed by paracentesis in these patients.

In a second report from the same laboratory W. J. Eisenmenger, S. H. Blondheim, A. M. Bongiovanni, and H. G. Kunkel (*J. Clin. Invest.* **29,** *1491 (1950)*) describe the mechanism of sodium retention during formation of ascites with decreased excretion of the electrolyte in urine, sweat and saliva. Retention occurs concurrent with reduction in serum concentrations of sodium as larger proportions of dietary sodium are utilized in formation of ascites. Moreover, it was observed that a decreasing tendency to form ascites was marked by a rise in serum sodium and increased urinary excretion of sodium, findings which often preceded clinically demonstrable changes in fluid balance.

A. V. N. Goodyer, A. S. Relman, F. D. Lawrason, and F. H. Epstein (*J. Clin. Invest.* **29,** *973 (1950)*) studied the renal phenomenon of salt retention in cirrhotics with

ascites. They found specific impairment of the mechanism within the kidney for excretion of intravenously administered sodium. In patients included in this study there was no demonstrable defect in glomerular filtration rates or in renal plasma flow. Retention, therefore, seemed to be accounted for by an increase in tubular reabsorption of the electrolyte.

These reports designate the importance to be assigned to electrolyte factors in the formation of ascites. Moreover, they add another food constituent which should be controlled in the dietary treatment of cirrhosis. Certainly every patient with ascites should have the benefit of therapeutic trial on diets restricted in content of salt before other more heroic approaches in therapy are attempted. If only to obviate the loss of fluid, minerals and protein through frequent paracenteses, the use of sodium restriction is warranted. Dietary restriction of salt is commonly utilized in modern therapy of cardiac edema and hypertension. Adequate control and avoidance of sodium deficiency may be achieved through the use of recently perfected and simplified laboratory methods of analysis of electrolytes in body fluids.

Evidence is accumulating that although many factors may function to favor the development of ascites in cirrhosis, control may be achieved by manipulation of those factors which are readily influenced by diet. In addition to the favorable reports of the clinical usefulness of sodium restriction, it should be recalled that ascites formation has been controlled by provision of high protein, low sodium diets to dogs in which portal stasis has been produced experimentally by the application of constricting aluminum bands about the inferior vena cava (*Nutrition Reviews* **7,** *26 (1949)*).

ABSORPTION AND EXCRETION OF VITAMIN B_{12} IN RATS AND MAN

Although the importance of vitamin B_{12} in metabolism first became evident because of its effectiveness in control of pernicious anemia in man, it was soon found that the vitamin was a normal dietary requirement of man, chicks, rats, mice, and some bacteria, and that the primary defect responsible for the development of pernicious anemia in man was not a dietary restriction in intake of vitamin B_{12}, but rather a failure properly to absorb the vitamin present in the diet. Briefly, it appears that a proteinaceous component of normal gastric juice (the intrinsic factor) is required for the proper absorption of vitamin B_{12} from the diet, and that this substance is much lower (or lacking altogether) in patients with pernicious anemia, as compared with other people (*Nutrition Reviews* **8,** *165 (1950)*). In such patients, injected vitamin B_{12} is far more effective in control of pernicious anemia than is vitamin B_{12} administered with the ration. Injected or orally administered vitamin B_{12} are equally effective in promoting growth of rats fed thyroprotein-containing diets, indicating that the small amounts of the vitamin required for growth are readily absorbed by normal animals.

Several recent papers indicate that absorption of this vitamin from the digestive tract is limited even in normal individuals. B. F. Chow, L. Barrows, and C. Lang (*J. Nutrition* **42,** *405 (1950)*) compared the urinary excretion of vitamin B_{12} following oral or subcutaneous administration in adult rats. Oral administration of 10, 30, or 90 micrograms of vitamin B_{12} in a single dose led to no increase in the urinary excretion (determined microbiologically with *Lactobacillus leichmannii*) over the low levels (0.04 to 0.13 micrograms in twenty-four hours) excreted by control animals. When 270 micrograms were fed, a slightly increased excretion, 0.65 micrograms, occurred during the twenty-four

hours following administration of the dose, which decreased rapidly to basal levels. After 1000 micrograms of vitamin B_{12} were given orally, about 1 per cent of the administered dose appeared in the urine. Thus, even at very high levels of intake, only a small fraction of the administered vitamin appeared in the urine. A markedly different picture followed subcutaneous injection of the vitamin. For example, following injection of 10 micrograms, 8.0 micrograms appeared in the urine within eight hours, and a total of 9.4 micrograms appeared within twenty-four hours.

From these results it is certain that the fate of orally administered vitamin B_{12} differs from that of injected vitamin B_{12}. The failure of the vitamin administered by the former route to appear in the urine suggests that it was not absorbed from the intestinal tract. Less likely alternatives would be a more efficient storage of the orally administered vitamin within the body, or its excretion in a form not available to the test organism, *L. leichmannii*.

These alternatives were examined by B. F. Chow *et al.* (*Proc. Soc. Exp. Biol. Med.* **76,** *393* (*1951*)) with the help of vitamin B_{12}-containing radioactive cobalt. This was administered orally in a single dose of 0.89 mg. per rat. After three to four days the animals were killed, and the radioactivity of various organs, of urine, and of feces were determined. Of the vital organs, only the liver and kidney contained high amounts of radiocobalt, amounts equivalent to 4.3 and 4.2 micrograms, respectively, of the original vitamin. Other organs (brain, testes, heart, blood) contained very low but significant amounts of the vitamin, results which prove that *some* absorption of the administered dose did occur. The urinary excretion of radiocobalt was low, and the amount of vitamin B_{12} excreted by this route, as calculated from the radioactivity, correlated rather closely with the amount as determined microbiologically. The great bulk of the radiocobalt was found in the feces, a clear indication that only a small amount of the administered vitamin had been absorbed from the intestinal tract.

Results very similar to these have been obtained in male human subjects. B. F. Chow and associates (*Bull. Johns Hopkins Hosp.* **87,** *156* (*1950*); *J. Nutrition* **43,** *323* (*1951*)) showed that following administration of 500 micrograms of vitamin B_{12} neither normal individuals nor untreated pernicious anemia patients excreted vitamin B_{12} in the urine. In both types of experimental subjects striking increases in urinary excretion of vitamin B_{12} followed intramuscular or intravenous injections of much smaller quantities—50 to 100 micrograms—of the vitamin, almost all of which was excreted unchanged. Microbiologic assay of the feces of subjects given the vitamin orally showed that most of the vitamin was excreted via this route, *i.e.*, it had not been absorbed. D. R. Jutton and H. T. Parsons (*Fed. Proc.* **10,** *203* (*1951*)) report similar results from oral versus intramuscular injection of the vitamin into women, again as assessed by microbiologic assay. By means of an entirely independent chemical method, G. E. Boxer and J. C. Rickards (*Arch. Biochem.* **30,** *392* (*1951*)) also report prompt urinary excretion of 90 to 95 per cent of a subcutaneously administered dose (1.08 mg.) of vitamin B_{12}; half of this was excreted three to five hours following injection, and most of it within twelve hours. Such prompt excretion following injection suggests a lack of facilities for storage of the vitamin, as well as a considerable degree of stability within the body.

It thus appears that both in normal rats and man only limited absorption of vitamin B_{12} can occur. Nevertheless, the little evidence available from experiments with rats indicates that when the magnitude of the amounts fed is similar to the metabolic requirement, essentially quantitative absorption occurs, since under these conditions orally administered and injected vitamin B_{12}

have equal growth-promoting activities. From these facts, and from what is known of the etiology of pernicious anemia, it is tempting to speculate that interaction of vitamin B_{12} with the intrinsic factor may be a prerequisite for absorption, and that the amount of vitamin B_{12} which can be absorbed is limited by the amount of intrinsic factor formed by a given organism. Such a self-imposed restriction on absorption would explain efficient absorption of trace amounts of the vitamin, and the very inefficient absorption of larger amounts, both of which have now been observed. Further work will undoubtedly clarify these interesting and unusual relationships.

VITAMIN DEFICIENCY SIGNS DURING ANTIBIOTIC THERAPY

The synthesis of vitamins by bacteria present in the gastrointestinal tract has been well demonstrated in certain species, particularly the rat (D. Melnick and B. L. Oser, *Vitamins and Hormones* **5,** *39* (*1947*)). Deficiency syndromes have also been produced in rats by the administration of sulfonamides in conjunction with purified synthetic diets (*Nutrition Reviews* **2,** *221* (*1944*)). The role of intestinal bacteria in the synthesis and utilization of vitamins in the human, however, has not been as conclusively established. With the discovery of agents such as aureomycin, chloramphenicol, and terramycin, which are even more effective than the sulfonamides in altering or even eliminating the usual bacterial flora of the intestine, the question of induced deficiency disease in the course of antibiotic therapy has been raised (Z. A. Leitner, *Brit. Med. J.* **1,** *491* (*1950*); H. Brainerd *et al.*, *J. Clin. Invest.* **28,** *992* (*1949*)). Although it is difficult to distinguish between deficiency resulting from drug-induced anorexia, vomiting, and diarrhea and that due to bacterial floral change, suggestive deficiency signs have been reported in patients receiving antibiotics (H. J. Harris, *J. Am. Med. Assn.* **142,** *161* (*1950*)), and routine vitamin supplementation has been recommended by P. H. Long and his co-workers (*Ibid.* **141,** *315* (*1949*)).

A noteworthy example of vitamin deficiency manifestations occurring during prolonged antibiotic therapy is a case reported by H. M. Gewin and G. J. Friou (*Yale J. Biol. Med.* **23,** *332* (*1951*)). Their patient was a 22-year-old man under treatment for subacute bacterial endocarditis due to a penicillin-resistant *Staphylococcus aureus*. Bacteremia persisted during thirteen days of aureomycin therapy (3.0 g. daily) and therefore chloramphenicol (3.0 g. daily) was used in addition to aureomycin for twenty days more. Anorexia, vomiting and diarrhea were present for four days before therapy was stopped and persisted for four more days. Recurrence of the bacteremia necessitated reinstitution of treatment in the same dosage six days later. The second course of combined antibiotics was continued for forty-six days. Two multivitamin capsules were given daily during the first course and the first thirteen days of the second course. Erythema and excoriation of the periscrotal skin occurred on the fourth day of the second course, and recurrent anorexia and vomiting began on the thirteenth day.

After eighteen days, evidences of vitamin deficiency were noted, consisting of a red, smooth tongue, diffuse pharyngeal injection, and desquamating yellowish papules about the nose and ears. Simultaneously, symmetrical scaling yellowish areas were seen in the groin and axillae. Marked improvement in these signs occurred within three days when a liquid mixture of vitamins A and D, thiamine, riboflavin, ascorbic acid and nicotinamide was given. However, vomiting of bloody material began on the thirty-sixth day, at which time prolonged prothrombin

time, liver enlargement and abnormal function tests were found. Gradual improvement over the next eight days accompanied the use of large doses of vitamin K, liver extract, B vitamins, and ascorbic acid administered intramuscularly. Atypical small bowel pattern with segmentation of barium was found on x-ray at this time.

Although antibiotics were stopped shortly thereafter, the patient complained of visual disturbances and numbness and tingling of his feet ten days later, with some areas of diminished pain sensation of the legs and feet. The visual changes disappeared, but over the next five weeks the peripheral neuritis symptoms and signs became more severe despite oral vitamin capsules and thiamine supplementation. Injections of vitamin B_{12} totaling 120 micrograms were given with subsequent progressive improvement. Complete reversal of symptoms occurred three months after antibiotic therapy had been concluded.

The authors point out that the occurrence of mucous membrane, skin, eye, neurologic and hematologic signs of deficiency disease in this patient may have been produced either by destruction of intestinal bacteria important in the synthesis or utilization of B vitamins, or by competitive blocking of intracellular metabolism. However, insufficient emphasis appears to have been laid upon the factors of anorexia, vomiting and diarrhea which are common in the use of these antibiotics. In a patient with severe illness of long duration such mechanisms might well precipitate deficiencies without resulting in incriminating changes in bacterial flora or intermediary metabolism. The validity of the mucous membrane and skin signs of deficiency may be questioned in view of the production of similar lesions during fungus infections. In fact, Harris (*loc. cit.*) frequently found *Monilia* in involved areas in antibiotic-treated patients. The association of deficiency signs in other organs in this patient, however, would appear to diminish this possibility.

Another hypothetical factor in the deficiency syndrome thus produced involves the fact that marked growth of yeast in the feces of patients receiving aureomycin and chloramphenicol is a common finding. (H. R. Bierman and E. Jawetz, *J. Lab. Clin. Med.* **37,** *394* (*1951*)). H. T. Ness, E. L. Price, and H. T. Parsons (*Science* **103,** *198* (*1946*)) found that the feeding of live yeast to human subjects was able to render thiamine unavailable for absorption, and that urinary excretion values of thiamine decreased during yeast ingestion. Thus it may be possible not only that the antibiotic therapy produces a decreased synthesis of thiamine but that the growth of yeast actually produces a state wherein orally administered thiamine is unavailable.

This case is but a suggestive example of the possible nutritional effects of antibiotic administration to humans. With the increasing use of these agents over longer periods of time it may be expected that more such cases will be seen. Studies of vitamin metabolism and excretion in patients receiving these agents are clearly indicated.

COTTONSEED MEAL

Cottonseed meal has been used extensively as a source of protein in livestock feeds for many years, and the proteins of cottonseed have a high nutritive value. Deleterious physiologic effects are noted, however, if cottonseed meal is not sufficiently heat-treated or treated with appropriate solvents to destroy or remove gossypol, a toxic compound. Gossypol is a polyphenol and is present in the pigment-gland fraction of the meal. Methods that have been used to detoxify cottonseed meals include ordinary

cooking, autoclaving, air oxidation, or oxidation by adding iron salts.

The pigment glands of cottonseeds are mechanically very strong and are very resistant to the action of most solvents. Ordinary methods of extraction for the removal of cottonseed oil, therefore, do not remove the toxic compound to any great extent. However, a flotation process has been devised that separates the pigment glands from cottonseed meal (H. L. E. Vix *et al.*, *J. Am. Oil Chem. Soc.* **24,** *228 (1947)*). Pigment gland-free cottonseed meal prepared by this process has been reported to be free of toxicity and can serve as a protein supplement in poultry rations (A. C. Groschke, M. Rubin, and H. R. Bird, *Poultry Sci.* **26,** *310 (1947)*); C. H. Boatner *et al.*, *Ibid.* **27,** *315 (1948)*). The observation by Boatner and associates that pigment glands were more toxic than pure gossypol when mixed into chick mash was assumed by Groschke and his co-workers to indicate that pure gossypol is detoxified when incorporated in a mixed feed.

The availability of relatively pure cottonseed pigment glands has stimulated investigations concerned with the physiologic effects of the pigment glands as compared with pure gossypol. R. J. Lillie and H. R. Bird (*Poultry Sci.* **29,** *390 (1950)*) compared the toxicity of pure gossypol and pigment glands of known gossypol content. These substances were administered daily by capsule at levels ranging from 5 to 40 mg. of gossypol per 100 g. body weight to 2-week-old chicks that were on diets composed principally of corn and soybean meal.

From the growth data it was apparent that the extent of growth depression was directly proportional to the gossypol intake whether gossypol was supplied in pure form or in the form of pigment glands. The toxicity of the pigment gland could therefore be accounted for by its gossypol content.

Recently A. M. Ambrose and D. J. Robbins (*J. Nutrition* **43,** *357 (1951)*) have reported the results of a study concerned with the toxicity of cottonseed pigment glands for the rat. These workers fed young weanling male rats a commercial dog ration supplemented with either processed cottonseed meals, cottonseed pigment glands, or pure gossypol. To determine the specific influence of pigment glands or pure gossypol on growth inhibition, the paired feeding technic was employed. Acute and subacute toxicities were also established by feeding pigment glands or pure gossypol via stomach tube.

Rats on the diets containing as much as 32 per cent of gland-free cottonseed meal exhibited no sign of toxicity. This meal had been rendered free of pigment glands by the flotation process of Vix and associates (*loc. cit.*) and contained 0.057 per cent of gossypol.

Meal prepared by hexane extraction (gossypol content, 1.10 per cent), when fed at a 15 per cent level in the diet definitely suppressed growth.

When cottonseed-meal pigment glands (sample 1) were fed at a level of 0.256 per cent of the ration (equivalent to 0.096 per cent gossypol in the diet), a definite growth inhibition occurred. A second sample of pigment glands fed at the same level and containing essentially the same amount of gossypol as sample 1 failed to inhibit growth. An explanation offered by the authors for the difference in toxicity between the two samples was that the gossypol may either deteriorate or become altered upon storage, since the sample showing lower toxicity was from seeds that were processed about six months after the first sample was processed. The authors raise the question of whether or not chemical assay for gossypol is reliable since both of these samples upon chemical assay were found to be about the same in gossypol content.

The influence of cottonseed pigment glands on reproduction in the rat was also investigated. Male and female rats on diets containing 0.256 per cent of cottonseed pig-

ment glands for one hundred days failed to reproduce. When such females were mated with normal males, they produced normal litters; however, only one litter of 6 survived. From the limited data, it would appear that spermatogenesis was adversely influenced but that ovulation was not.

In the paired feeding studies there was a direct correlation between the level of pigment gland fed and the degree of growth inhibition. The depressive effect on growth was most pronounced during the first fifteen days of the fifty-eight day experimental period. Paired-fed controls were limited in food intake to the amount consumed by those receiving either pigment glands or pure gossypol in the diet, and in all cases the controls made body weight gains considerably better than their respective mates. The growth inhibition of the gossypol or pigment gland-fed rats could not be accounted for on the basis of reduced food intake alone. It was therefore implied that gossypol played an important role as a growth-depressing agent.

The results with single doses indicated that cottonseed pigment glands and gossypol possess rather low acute toxicities for the rat. Doses of 300 mg. of gossypol per 100 g. body weight were nontoxic. In contrast, 6 mg. per 100 g. body weight per day administered over a period of fifty-eight days depressed growth and did not permit normal body weight gains even after the gossypol was withdrawn.

E. Eagle and H. F. Bialek (*Food Research* **15,** *232 (1950)*) also investigated the effect of gossypol and cottonseed pigment glands on the rat. These workers noted that the efficiency of cottonseed pigment glands as growth inhibitors was closely correlated with the gossypol content, but that the acute toxicities were different. For example, a sample of pigment glands that contained 40 per cent of gossypol (LD_{50} 1140 mg. per kilogram body weight) was almost two and one-half times as toxic as a sample of pure gossypol (LD_{50} 2800 mg. per kilogram body weight).

Suggestive evidence is thus accumulating that there may be alterations in cottonseed pigment glands, unrelated to their gossypol content as determined by chemical assay, and that these alterations somehow influence their physiologic effects. As a matter of nutritional interest, it would appear that cottonseed meals prepared by a process whereby the pigment glands are removed from the meal would be the preferred process. This is true for several reasons. Such meals have been found to be nontoxic in animal studies, and they have a more attractive appearance since most of the dark color in cottonseed is removed with the pigment glands.

Gossypol possesses antioxidant properties (*Nutrition Reviews* **3,** *167 (1945)*) and it has been suggested that it might therefore serve a valuable purpose if present in small proportions in mixed feeds. Because of its appetite-inhibiting properties, it has also been suggested that this compound might be of use in the control of obesity in man. The recent studies, however, reaffirm the more generally accepted belief that gossypol is a toxic compound and therefore probably will have no practical value in the control of obesity or as an antioxidant. Further studies are obviously needed to clarify some of the conflicting reports concerning the toxicity of cottonseed pigment glands.

NOTES

Teaching Nutrition on a Global Scale

Agricultural and economic considerations are of paramount importance wherever nutritional improvements are considered. Obviously, satisfactory diets cannot be evolved unless the foodstuffs which will provide the required nutrients are available. On the other hand, while the availability of these foodstuffs is a prerequisite to establishment of better dietaries, it is not a sufficient condition. Knowledge of nutritional principles, sound planning of distribution and conservation, and proper methods of processing are also necessary if full use of the available supplies is to be made. If shortages are present or threaten, still greater knowledge and care are needed to minimize the effects of these unfavorable circumstances. Thus, while nutrition education at all levels, from that of technical advisers to governments to that of consumers, is important in times of plenty, it becomes essential in times of restrictions.

It is thus natural that the Nutrition Division of the Food and Agriculture Organization has emphasized nutrition education in all of its field programs. To guide its technical assistance officers, as well as to popularize recent advances in nutrition education, one of the members of the Division, J. A. S. Ritchie, has prepared a manual ("Teaching Better Nutrition—A Study of Approaches and Techniques," *FAO Nutritional Studies, No. 6, Washington, D.C. (Nov. 1950)*) which now can be considered the classic work in this field. Well qualified for such a global approach by her diverse experience as a field worker in Scotland, the United States, and England, as an official with the United Kingdom Ministry of Food during World War II, as an UNRRA missionary to Poland and Yugoslavia during the immediate postwar periods, and for several years as a member of the FAO Nutrition Division with field experience in Europe, Latin America, and the Far East, Miss Ritchie brings to this work the merit of fully appreciating the differences in approaches and technics which differences in geographic, economic, political, and cultural patterns make necessary, while emphasizing the fundamental principles applicable to all situations.

The first part of the manual deals with what have come to be known as the factors of "cultural anthropology" in food patterns and nutrition. The cultural significance of food in various civilizations, including such considerations as familiarity, prestige values, religious restrictions, superstitions, and prejudices are carefully examined in the light of numerous examples. The psychologic implications of these factors in terms of resistance to alterations of food habits are next discussed. Thus from the very start, the reader is reminded that knowledge of education is as important as knowledge of nutrition if the venture in nutrition education is to succeed. Next come technical considerations on collecting background information for a nutrition program, including methods of study of food habits, sampling, and collection of consumption data, evaluation of the dietaries, and technics of mass assessment of nutritional status.

The second chapter of the manual deals with the organizational aspects of nutrition education, both on the communal and national scale. Miss Ritchie makes full use of the wealth of information sent annually to FAO by sixty-odd governments. The advantages of various approaches, for instance, through the medical profession, agricultural and home-improvement services, schools, and commercial companies are discussed in the light of numerous examples of highly, moderately, or less developed countries.

The aims and methods of training of nutrition workers are described and discussed in the third chapter. Many different classes of individuals—nutritionists, dietitians, practitioners, public health workers, nurses, welfare officers, teachers, administrators, and

agronomists should receive training in nutrition. This can be done in academic institutions, in long-term in-service conditions, through short courses, or in nutrition workshops such as that organized by Dr. Lydia Roberts in the Home Economics Department of the University of Puerto Rico. Training of local leaders, particularly in underdeveloped areas, can also be effected either in long- or in short-term courses.

The fourth and fifth sections, dealing with teaching methods and materials, are particularly valuable to the active educationalist. At no time are the fundamental objectives or the practical difficulties forgotten as the author discusses an impressive list of topics: surveys as teaching mediums, home visits, advisory centers, clinics, demonstrations, lectures, nutrition courses for the general public, discussion meetings and group decisions, education through group feeding, nutrition education in schools, community programs. A rational and suggestive description of the use of teaching aids, such as films, film strips, lantern slides, posters, charts, exhibitions, plays and puppet shows, demonstration gardens, publications, circular letters, and radio is given with numerous and apt examples for each main type of situation.

No program is complete without evaluation of results. Chapter 6 provides objective methods of evaluation, including choice of the yardsticks and the methods of meanings. The last section includes detailed analysis of characteristic results achieved in typical areas through various methods. They are termed suggestively: the agricultural approach—Iran; the rural school approach—Guatemala; the approach through literacy campaigns—Nigeria; the citizens' government approach—The Netherlands; the home economics approach—Puerto Rico; the "food for family" campaign—Jamaica; rural center approach—India.

The development of certain technics and disciplines and their recognition as valid entities has often been, in the past, the direct consequence of publication of a clear, popular textbook on the subject. It may be said that with publication of the FAO manual, nutrition education has "come of age", because the universal characteristics of nutrition education, independent of local conditions, have been squarely brought out and strikingly illustrated. Besides being a precious guide to specialists, this manual should help "nonspecialized" persons to recognize nutrition education as an essential branch of health education.

Symposium on Antimetabolites

Under the chairmanship of D. W. Woolley, and the sponsorship of the New York Academy of Sciences, an excellent symposium on antimetabolites was held and has been gathered together in a monograph on the subject (*Ann. N. Y. Acad. Sci.* **52,** *1197 (1950)*). The monograph consists of thirteen papers including some on the general topic of antimetabolites, their biologic actions, biochemical significance, and utilization in the study of biologic problems, and, in addition, studies of the para-aminobenzoic acid-sulfonamide competition, of amino acid antagonists, and of pyridoxine and pteroylglutamic acid antagonists. The results of the use of pteroylglutamic acid analogues in experimental tumors are also presented.

Chaucer and Nutrition

"If a man knew how many maladyes
Follow excesse and wyn and glotonyes,
He wolde be the more mesurâble
Of his diete, sittyng at his table.
Allas! the shorte throte, the tendre mouth,
Maketh the Est and West, and North and South,
In erthe, in watir, in ayer, man to sweat,
To get a sely glotoun drynke and mete."

—The Pardoneres Tale in "Chaucer's Canterbury Tales," *Everyman's Library, J. M. Dent and Sons, London (1910)*